DOI: 10.1111/j.1468-1293.2010.00885.x

ORIGINAL RESEARCH

Efficacy, tolerability and risk factors for virological failure of darunavir-based therapy for treatment-experienced HIV-infected patients: the Swiss HIV Cohort Study

J Young,[1] AU Scherrer,[2] HF Günthard,[2] M Opravil,[3] S Yerly,[4] J Böni,[5] M Rickenbach,[6] CA Fux,[7] M Cavassini,[8] E Bernasconi,[9] P Vernazza,[10] B Hirschel,[11] M Battegay[12] and HC Bucher[1,12] for the Swiss HIV Cohort Study*

[1]Basel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, Basel, Switzerland, [2]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, Zurich, Switzerland, [3]Division of Infectious Diseases, Hirslanden Clinic Aarau, Aarau, Switzerland, [4]Laboratory of Virology, Geneva University Hospital, Geneva, Switzerland, [5]Swiss National Centre for Retroviruses, Institute of Medical Virology, University of Zurich, Zurich, Switzerland, [6]Swiss HIV Cohort Study Co-ordination Centre, University Hospital Lausanne, Lausanne, Switzerland, [7]Division of Infectious Diseases, University Hospital Bern and University of Bern, Bern, Switzerland, [8]Division of Infectious Diseases, University Hospital Lausanne, Lausanne, Switzerland, [9]Regional Hospital of Lugano, Lugano, Switzerland, [10]Division of Infectious Diseases and Hospital Epidemiology, Cantonal Hospital, St Gallen, Switzerland, [11]Division of Infectious Diseases, University Hospital Geneva, Geneva, Switzerland and [12]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Basel, Switzerland

Objectives

Darunavir was designed for activity against HIV resistant to other protease inhibitors (PIs). We assessed the efficacy, tolerability and risk factors for virological failure of darunavir for treatment-experienced patients seen in clinical practice.

Methods

We included all patients in the Swiss HIV Cohort Study starting darunavir after recording a viral load above 1000 HIV-1 RNA copies/mL given prior exposure to both PIs and nonnucleoside reverse transcriptase inhibitors. We followed these patients for up to 72 weeks, assessed virological failure using different loss of virological response algorithms and evaluated risk factors for virological failure using a Bayesian method to fit discrete Cox proportional hazard models.

Results

Among 130 treatment-experienced patients starting darunavir, the median age was 47 years, the median duration of HIV infection was 16 years, and 82% received mono or dual antiretroviral therapy before starting highly active antiretroviral therapy. During a median patient follow-up period of 45 weeks, 17% of patients stopped taking darunavir after a median exposure of 20 weeks. In patients followed beyond 48 weeks, the rate of virological failure at 48 weeks was at most 20%. Virological failure was more likely where patients had previously failed on both amprenavir and saquinavir and as the number of previously failed PI regimens increased.

Conclusions

As a component of therapy for treatment-experienced patients, darunavir can achieve a similar efficacy and tolerability in clinical practice to that seen in clinical trials. Clinicians should consider whether a patient has failed on both amprenavir and saquinavir and the number of failed PI regimens before prescribing darunavir.

Keywords: Bayes theorem, HIV drug resistance, protease inhibitors, risk factors, salvage therapy, viral load

Accepted 13 July 2010

Correspondence: Dr James Young, Basel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, Hebelstrasse 10, Basel CH-4031, Switzerland. Tel: + 41 61 265 3100; fax: + 41 61 265 3109; e-mail: jyoung@uhbs.ch

*See Appendix.

Introduction

Patients with multi-drug-resistant HIV now have a number of treatment options, including the protease inhibitors (PIs) darunavir and tipranavir, the nonnucleoside reverse transcriptase inhibitor (NNRTI) etravirine, the integrase inhibitor raltegravir, the chemokine (C-C motif) receptor 5 (CCR5) antagonist maraviroc and the fusion inhibitor enfuvirtide [1]. Darunavir, a second-generation PI, was designed for PI-resistant HIV [2]. After 48 weeks of treatment with darunavir, 45% of highly treated patients achieved a viral load below 50 HIV-1 RNA copies/mL [3], with this percentage rising to 71 and 84% in moderately treated and treatment-naïve patients, respectively [4,5]. After treatment failure on multiple regimens, patients should be given a salvage therapy with at least two active drugs [6], and use of darunavir in combination with etravirine, enfuvirtide or raltegravir improves efficacy [3,7–9]. Mutations resistant to darunavir [10–14], while infrequent, are more prevalent after treatment failure on amprenavir or saquinavir and as the number of failed PI regimens increases [15].

Darunavir has shown good results in clinical trials but few data are available from clinical practice. We report on the efficacy and tolerability of darunavir in the Swiss HIV Cohort Study (SHCS) as a salvage therapy for treatment-experienced patients and we assess risk factors associated with its virological failure.

Methods

Patients

The SHCS is a prospective cohort with continuing enrolment of HIV-infected adults [16]. Our population of interest was all patients in the SHCS whose first use of darunavir was as a component of salvage therapy. We defined a salvage therapy as any therapy used after a patient recorded a viral load above 1000 copies/mL given prior exposure to PI- and NNRTI-based therapies for more than 90 days each. Our sample from this population was all those with viral load and CD4 cell count measured up to 180 days before starting darunavir, and with at least one viral load measured 12 weeks or more after starting darunavir. We followed the patients in this sample for up to 72 weeks.

Virological failure

Virological failure is the failure to achieve viral suppression or viral rebound after suppression. In clinical trials of antiretroviral drugs, virological failure is often assessed during 48 weeks of follow-up according to the Food and Drug Administration's (FDA) time to loss of virological response algorithm [17]. Their algorithm is not well suited to this study because scheduled follow-up visits in the SHCS are 6 months apart, so viral suppression or viral rebound may go undetected if two consecutive measurements are required either below or above some threshold, respectively. We assessed failure in each of three periods: 0 to 24 weeks, >24 to 48 weeks, and >48 to 72 weeks. Any patient with no visit in one period who then failed in the next period was assumed to have first failed in the preceding period with no visit.

We assessed virological failure using three variants of the FDA's algorithm. In all variants, death or a clinician stopping the use of any drug because of 'treatment failure' was also considered a failure. In the first variant, viral suppression was defined as the first of two consecutive viral load measurements below 50 copies/mL; viral rebound was defined as the first of two consecutive viral load measurements of 50 copies/mL or more after suppression. In the second variant, viral suppression was defined as a first viral load measurement below 50 copies/mL; viral rebound was defined as a first viral load measurement of 400 copies/mL or more after suppression. The third variant used the same definitions as the second but, in addition, stopping the use of darunavir for any reason was also considered a failure.

Risk factors for virological failure

We considered risk factors for virological failure suggested by the PLATO II multi-cohort collaboration [18]. In PLATO II, the rate of virological failure for patients starting a second therapy with a boosted PI (after failing a first therapy with an NNRTI) was lower for homosexual men, for those with lower viral load and higher CD4 cell count when starting the second therapy, and for those who spent less than 3 months on their first therapy after viral rebound and before starting the second therapy. There was also weak evidence that including a *de novo* nucleoside reverse transcriptase inhibitor (NRTI) in the second therapy was associated with a lower rate of virological failure.

These results suggest that a model for virological failure on salvage therapy should include measures of patient health, adherence to therapy and the potency of therapy. We used viral load and CD4 cell count when starting salvage therapy as measures of patient health (and, if undetectable, viral load was set to the lower limit of detection). We defined poor adherence as either missing two doses in a row or missing a dose at least once a week (of any antiretroviral drug, not just darunavir) if this was reported at two or more of the last four visits prior to

starting salvage therapy. These variables are imperfect measures of patient health and adherence; therefore we also included the generic predictors age and gender in our model.

As a measure of the potency of therapy, we used an overall genotypic sensitivity score (GSS) based on a cumulative analysis of all resistance tests made prior to starting darunavir. Genotypic data were extracted from the SHCS resistance database (SmartGene IDNS version 3.5.6; SmartGene, Zug, Switzerland) which contains all genotypic HIV resistance tests performed by the four authorized laboratories in Switzerland [19]. A GSS was defined for each NRTI, NNRTI and PI using the Stanford algorithm (version 6.0.3), such that 0 denotes full resistance to a given drug, 0.5 denotes intermediate resistance and 1 denotes full susceptibility. Raltegravir and enfuvirtide were deemed fully susceptible if no mutation in the International AIDS Society (IAS)-USA mutation list was detected in integrase and glycoprotein 41 (gp41) tests, respectively [20]; or in the absence of these tests, full susceptibility was assumed for these drugs (and for maraviroc) unless these drugs had already been used in a failed regimen. To derive an overall GSS for therapy, we summed the scores of each drug in the regimen.

We also considered a number of alternatives to this overall GSS, to see if these alternatives suggest some simple rules for clinical practice. First, we replaced the overall GSS with two components – a GSS for darunavir and a GSS for background therapy. Secondly, we considered whether each of these component GSS values can be approximated by simple clinical measures. As rough measures of existing resistance to darunavir, we assessed whether the patient failed on both amprenavir and saquinavir and counted the number of failed PI regimens. As rough measures of the potency of background therapy, we assessed whether the patient had at least one other second generation antiretroviral in the regimen in addition to darunavir and counted the number of *de novo* drugs in the regimen in addition to darunavir.

Time to event analyses

With limited data for analysis, we took a Bayesian approach to fitting Cox proportional hazards models for time to virological failure. Given that we assessed failure in each of three periods, we used a discrete time version of the Cox model with an offset that adjusts for variation in the time between assessments [21]. For each predictor in our model, we asserted a 'vaguely informative' prior where 'the percentiles of the prior distribution would be viewed as at least reasonable if not liberally inclusive by all those working in the research topic' [22]. Each prior was represented by a lognormal distribution for a hazard ratio, data that reproduced this distribution were added to the observed data, and standard software was then used to estimate an approximate posterior hazard ratio by a weighted averaging over observed and prior data with each set of prior data assigned to a separate stratum [23].

A priori, we classified each predictor into one of five categories. First we rescaled continuous predictors age, viral load and CD4 cell count into clinically meaningful units (per 10 years, $\log_{10}$ copies and 100 cells/μL, respectively) and centred each about its median. Age and gender were then classified as having effects on virological failure of 'uncertain direction' with a median [95% confidence interval (CI)] prior hazard ratio of 1.0 (0.25–4) [23]. The effects of viral load and CD4 cell count when starting salvage therapy were classified as 'possibly harmful' and 'possibly beneficial' with median hazard ratios of 1.5 (95% CI 0.38–6) and 0.67 (95% CI 0.17–2.7) and with probabilities of being above 1 of 0.72 and 0.28, respectively. Poor adherence and overall GSS were classified as 'probably harmful' and 'probably beneficial' with median hazard ratios of 2.0 (95% CI 0.5–8) and 0.5 (95% CI 0.13–2) and with probabilities of being above 1 of 0.84 and 0.16, respectively. These priors correspond to normal distributions for the log hazard ratio with variance 0.5 [23], and the normal cumulative distribution function was used to calculate the probability of a hazard ratio above 1.

When considering alternatives to the overall GSS, we compared models using twice the log Bayes factor (2logBF) with the integral of a posterior density calculated by Laplace's method of approximation [24]. We used SAS version 9.1.3 (SAS Institute Inc., Cary, NC, USA) for our analyses.

Results

Patients

As of February 2009, 196 patients in the SHCS had started darunavir for the first time but only 130 patients started darunavir as part of a salvage therapy. Of these 130 patients, 115 (88%) had at least one viral load measured 12 weeks or more after starting.

Patients starting darunavir as part of a salvage therapy (Table 1) had a median age of 47 years and had been living with HIV for a median of 16 years. Most (81%) received mono or dual antiretroviral therapy prior to starting highly active antiretroviral therapy and since then had experienced virological failure on a median of three PI-based regimens. Prior to starting darunavir, 77% of patients had been given lopinavir, with 52% recording a viral load above 1000 copies/mL while on a regimen that included this drug. Typically, a considerable period had elapsed

Table 1 Patient characteristics when starting darunavir as part of a salvage therapy

Characteristic	Population ($n = 130$)*	Sample ($n = 115$)*
Demographics		
Age (years) (median)	47	47
Female (%)	19	18
Heath status		
CD4 cell count (cells/μL) (median)	250 (3)	250
Log_{10} HIV RNA (copies/mL) (median)	3.5 (3)	3.4
Undetectable viral load (median)	20 (3)	21
Clinical stage CDC group C (%)	43	42
Hepatitis C (%)	22	22
History of infection and treatment		
Transmission by injecting drug use (%)	14	16
Reported duration of infection (years) (median)	16.4 (20)	16.4 (15)
Time since first treatment (years) (median)	12.2	12.2
Mono or dual therapy prior to starting HAART (%)†	81	82
Time since triple class failure (years) (median)‡	6.6	6.6
Time at risk since triple class failure (years) (median)§	3.6	3.5
Number of failed PI regimens (median)	3	3
Number of resistance tests prior to starting darunavir¶ (median)	–	4
Time since last test when starting darunavir (weeks) (median)	–	27
Full susceptibility to darunavir when starting (%)	–	42
Full resistance to darunavir when starting (%)	–	6
Overall GSS when starting darunavir‖ (median)	–	2
Number of *de novo* drugs when starting darunavir** (median)	3	3
Number of drugs in regimen when starting darunavir** (median)	5	5
Risk behaviours reported at the most recent follow-up		
Appreciable nonadherence (%)††	10 (1)	10 (1)
Attending a drug substitution programme (%)	11 (40)	9 (38)
Illegal drug use (%)	18 (45)	17 (43)

*If not available for all patients, then the number of missing observations is given in parentheses.
†First therapy: 19% HAART, 48% monotherapy with zidovudine, 18% dual therapy with two nucleoside reverse transcriptase inhibitors (NRTIs), and 15% other [monotherapy with either some other NRTI or a protease inhibitor (PI), or dual therapy with a PI and an NRTI].
‡Time since first viral load above 1000 copies/mL given prior exposure to both PI- and nonnucleoside reverse transcriptase inhibitor (NNRTI)-based therapies for more than 90 days.
§Time on therapy with a viral load above 400 copies/mL between a first triple class failure and starting darunavir.
¶Number of polymerase tests; only assessed for patients in the sample.
‖GSS for each drug (where 0 is full resistance, 0.5 is intermediate resistance and 1 is full susceptibility) summed for all drugs in the regimen; only assessed for patients in the sample.
**Includes darunavir.
††At the last follow-up visit, patient reports missing two doses in a row or missing a dose at least once a week.
CDC, Centers for Disease Control and Prevention (www.cdc.gov); HAART, highly active antiretroviral therapy; GSS, genotypic sensitivity score; PI, protease inhibitor.

between assumed 'triple class failure' (i.e. first reporting a viral load above 1000 copies/mL given prior exposure to PI- and NNRTI-based therapies for more than 90 days each) and starting darunavir (median 6.6 years), and much of this period (median 3.6 years) was spent at risk of developing resistant mutations, with the patient on therapy while having a viral load above 400 copies/mL. When starting darunavir, only 42% of patients had HIV considered fully susceptible to darunavir. Patients started in reasonable health (median CD4 count 250 cells/μL) given that many patients had an advanced infection [43% Centers for Disease Control and Prevention (CDC) group C] and a relatively high proportion (22%) were coinfected with hepatitis C virus.

Initial salvage therapy and changes to therapy

These 130 patients began salvage therapy with 80 different treatment combinations; however, 71% received two or more nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) and 77% received at least one other second-generation antiretroviral in addition to darunavir (raltegravir, 54 patients; etravirine, 39 patients; enfuvirtide, 37 patients; maraviroc, nine patients; vicriviroc, one patient) with a median of five drugs in the regimen.

During a median patient follow-up period of 45 weeks, 22 of 130 patients stopped taking darunavir after a median exposure of 20 weeks, although later 12 patients restarted darunavir. None of these patients stopped taking darunavir because of 'treatment failure'. Three patients were lost to follow-up, 13 patients stopped for unspecified reasons (10 later restarted darunavir) and the remaining six patients stopped because of adverse events – abnormal fat distribution (two patients), liver toxicity (two patients), gastrointestinal tract toxicity (one patient), and an unspecified toxicity (one patient), although these last two patients later restarted darunavir. Of the two patients who stopped because of liver toxicity, neither tested positive for hepatitis B or C.

Changes to therapy were common: 53 patients made a change of some sort on a median of two occasions. Among the 37 patients receiving enfuvirtide when starting darunavir, 22 were no longer receiving enfuvirtide at the end of follow-up and, of these, 11 had switched to raltegravir (all in combination with darunavir).

Adverse events

One of the patients restarting darunavir then stopped taking darunavir again and died 1 month later. The main cause of death was recorded as 'HIV disease resulting in other bacterial infections' [International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) code B20.1]. The patient had a history of virological failure on PI-based regimens (lopinavir, atazanavir and tipranavir) and never achieved viral suppression on darunavir. Of the 130 patients, four were diagnosed with either a new AIDS-defining disease or a relapse of such a disease after starting darunavir.

Virological failure

During a median patient follow-up period of 51 weeks, 115 patients had a median of four viral load measurements with a median interval between measurements of 9.4 weeks. Of the 571 viral load measurements, 88% were made using a Cobas-TaqMan 96 assay (Roche Molecular Diagnostics, Rotkreuz, Switzerland), 11% were made using an Amplicor ultra-sensitive assay (Roche Molecular Diagnostics) and only five measurements (<1%) were made using an Amplicor standard assay. Under the three variants of the FDA's algorithm, virological failure was seen in 20, 18 and 29 patients for the first, second and third variants, respectively (Table 2). Many of the patients who failed started darunavir with HIV mutations associated with resistance to darunavir: 11, 10 and 14 patients among those who failed (55, 56 and 48%, respectively) had at least one relevant mutation and a median of 3, 2 and 1.5 relevant mutations under the three variants, respectively.

Time to event analyses

We present full results of time to event analyses for the third variant (Table 3) because this variant leads to the greatest number of failures, increasing the information available for analysis. In the final column of Table 3, we attach our interpretation of the clinical meaning of the posterior hazard ratio and its 95% CIs. A comparison of prior and posterior meanings shows what a clinician with these prior opinions would learn from these data. He or she would now consider virological failure less likely in older patients and more likely in female patients; higher viral load and higher CD4 cell count when starting darunavir would now be seen as at most slightly increasing and slightly decreasing the risk of virological failure, respectively; but past poor adherence would still be viewed as probably harmful. He or she would now be less certain that an overall GSS when starting darunavir was predictive of subsequent virological failure.

Table 2 Number (and per cent) of patients failing in each of three periods under each of the three variants of the Food and Drug Administration's (FDA) time to loss of virological response algorithm

	Variant of the FDA's time to loss of virological response algorithm					
	Variant 1*		Variant 2†		Variant 3‡	
Weeks	Patients (*n*)§	Failed [*n* (%)]	Patients (*n*)§	Failed [*n* (%)]	Patients (*n*)§	Failed [*n* (%)]
0–24	115	18 (16)	115	10 (9)	115	18 (16)
>24 to 48	79	1 (1)	86	5 (6)	81	10 (12)
>48 to 72	53	1 (2)	54	3 (6)	48	1 (2)

Virological failure is the failure to achieve viral suppression or viral rebound after suppression (death or stopping the use of any drug where the reason given is 'treatment failure' is also considered a failure).
*Viral suppression is defined as the first of two consecutive viral load measurements below 50 copies/mL; viral rebound is defined as the first of two consecutive viral load measurements of 50 copies/mL or more after suppression.
†Viral suppression is defined as a first viral load measurement below 50 copies/mL; viral rebound is defined as a first viral load measurement of 400 copies/mL or more after suppression.
‡As for Variant 2 but, in addition, stopping the use of darunavir for any reason is also considered a failure.
§Patients with a viral load measured within a given period who did not fail in a previous period.

Table 3 Time to event analysis of risk factors for virological failure, with failure assessed using the third variant of the Food and Drug Administration's (FDA) time to loss of virological response algorithm

Model	Variant	Predictor	Prior median		ML estimate	Approximate posterior median	
			Meaning		Hazard ratio (95% CI)		Meaning
1	3	Age	Uncertain direction	1.0 (0.25, 4.0)	0.58 (0.35, 0.94)	0.60 (0.38, 0.94)	Certainly beneficial
		Female	Uncertain direction	1.0 (0.25, 4.0)	2.1 (0.83, 4.8)	1.7 (0.78, 3.7)	Probably harmful
		Viral load	Possibly harmful	1.5 (0.38, 6.0)	1.2 (0.91, 1.8)	1.3 (0.92, 1.7)	Weakly harmful
		CD4 cell count	Possibly beneficial	0.67 (0.17, 2.7)	0.92 (0.72, 1.1)	0.92 (0.72, 1.1)	Weakly beneficial
		Poor adherence	Probably harmful	2.0 (0.5, 8.0)	1.5 (0.43, 4.0)	1.7 (0.68, 3.7)	Probably harmful
		Overall GSS	Probably beneficial	0.50 (0.13, 2.0)	0.99 (0.64, 1.5)	0.93 (0.61, 1.4)	Uncertain direction

Full results are shown for model 1 where the potency of initial therapy is assessed using the overall genotypic sensitivity score (GSS). CI, confidence interval; ML, maximum likelihood; GSS, genotypic sensitivity score.

Table 4 Time to event analysis of risk factors for virological failure, with failure assessed using all three variants of the Food and Drug Administration's (FDA) time to loss of virological response algorithm

Model	Variant	Predictor	Prior median		ML estimate	Approximate posterior median	
			Meaning		Hazard ratio (95% CI)		Meaning
1	1	Overall GSS*	Probably beneficial	0.50 (0.13, 2.0)	0.66 (0.37, 1.1)	0.63 (0.36, 1.1)	Probably beneficial
	2				0.88 (0.49, 1.6)	0.80 (0.46, 1.4)	Possibly beneficial
	3				0.99 (0.64, 1.5)	0.93 (0.61, 1.4)	Uncertain direction
2	1	Background therapy GSS†	Possibly beneficial	0.67 (0.17, 2.7)	0.73 (0.38, 1.4)	0.70 (0.38, 1.2)	Probably beneficial
	2				1.1 (0.57, 2.3)	0.95 (0.52, 1.8)	Uncertain direction
	3				0.99 (0.59, 1.7)	0.95 (0.59, 1.5)	Uncertain direction
	1	Resistance to darunavir‡	Possibly harmful	1.5 (0.38, 6.0)	2.6 (0.50, 13)	1.8 (0.64, 5.4)	Probably harmful
	2				3.8 (0.62, 22)	2.0 (0.65, 6.1)	Probably harmful
	3				1.0 (0.24, 4.1)	1.2 (0.43, 3.2)	Uncertain direction
3	1	Another second-generation drug§	Possibly beneficial	0.67 (0.17, 2.7)	0.91 (0.35, 2.7)	0.82 (0.37, 1.9)	Uncertain direction
	2				0.96 (0.34, 3.2)	0.86 (0.38, 2.1)	Uncertain direction
	3				1.1 (0.46, 2.9)	0.94 (0.46, 2.0)	Uncertain direction
	1	Failed both APV and SQV	Possibly harmful	1.5 (0.38, 6.0)	2.3 (0.81, 6.1)	2.0 (0.87, 4.5)	Probably harmful
	2				2.6 (0.87, 7.2)	2.1 (0.90, 4.9)	Probably harmful
	3				2.2 (0.87, 5.1)	1.9 (0.90, 3.9)	Probably harmful
4	1	Number of *de novo* drugs¶	Possibly beneficial	0.67 (0.17, 2.7)	0.71 (0.43, 1.1)	0.71 (0.45, 1.1)	Probably beneficial
	2				0.72 (0.43, 1.2)	0.72 (0.45, 1.1)	Probably beneficial
	3				0.77 (0.52, 1.1)	0.77 (0.53, 1.1)	Probably beneficial
	1	Number of failed PI regimens	Possibly harmful	1.5 (0.38, 6.0)	1.5 (1.2, 2.1)	1.5 (1.2, 2.0)	Certainly harmful
	2				1.8 (1.3, 2.5)	1.7 (1.3, 2.4)	Certainly harmful
	3				1.3 (1.0, 1.7)	1.3 (1.0, 1.7)	Certainly harmful

The potency of initial therapy is first assessed by the overall genotypic sensitivity score (GSS) in model 1; this score is then replaced by three alternatives (in models 2 to 4), each alternative being a pair of predictor variables. All estimates are adjusted as in Table 3 for age, gender, viral load, CD4 cell count and previously reported poor adherence.
*GSS for each drug (where 0 is full resistance, 0.5 is intermediate resistance and 1 is full susceptibility) summed for all drugs in the regimen.
†Overall GSS minus GSS for darunavir.
‡GSS for darunavir re-coded so that 0 is full susceptibility, 0.5 is intermediate resistance and 1 is full resistance.
§Starting salvage therapy with darunavir plus *de novo* use of one or more of the drugs raltegravir, etravirine, enfuvirtide, maraviroc and vicriviroc.
¶Number of antiretrovirals in the regimen used for the first time in addition to darunavir.
CI, confidence interval; ML, maximum likelihood; GSS, genotypic sensitivity score; PI, protease inhibitor; APV, amprenavir; SQV, saquinavir.

However, under other variants of the FDA's algorithm, the overall GSS seems more predictive of virological failure (Table 4). Under the first two variants, patients who stop taking darunavir are not considered failures unless the reason given for stopping is treatment failure. Alternatives to the overall GSS suggest that both the number of failed PI regimens and failure on both amprenavir and saquinavir have some value as measures of the risk of virological failure, regardless of the variant used to assess failure. Compared with a model where the potency of therapy is measured by resistance tests (model 2), a model with binary clinical measures (model 3) is as good at predicting the observed data (with 2logBF of –0.1, 1.6 and 3.0 under the three variants, respectively) and a model with continuous clinical measures (model 4) is slightly better at predicting the observed data (with 2logBF of 4.4, 9.4 and 3.9 under the three variants, respectively) [24].

Discussion

The patients receiving darunavir as part of salvage therapy in this study were not dissimilar to the highly treated patients receiving darunavir in the POWER trials [3]. Our patients were slightly older (mean age 48 years *vs.* 44 years), had been infected with HIV for longer (mean duration 17 years *vs.* 12 years) and started darunavir with a more advanced infection (CDC group C 43% *vs.* 36%), and hepatitis was more prevalent in our patients (chronic hepatitis B or C 23% *vs.* 11%). Yet our patients started darunavir in a better state of general health, with a lower viral load (mean 3.4 *vs.* 4.6 log copies/mL) and a higher CD4 cell count (median 250 *vs.* 150 cells/μL). A similar proportion of patients in our study started darunavir with three or more major PI mutations (57% *vs.* 54%) and with three or more darunavir-associated mutations (17% *vs.*

22%). In the POWER trials, 55% of highly treated patients failed to achieve a viral load below 50 copies/mL after 48 weeks of treatment with darunavir [3]. In our study, 61 patients were followed for at least 48 weeks and at 48 weeks, 12 (20%) had experienced virological failure under the third variant of the FDA's algorithm. In the POWER trials, 21% of patients discontinued darunavir before 48 weeks [3]. In our study, seven (11%) of the 61 patients followed for at least 48 weeks had discontinued darunavir before 48 weeks. Note that, in our study, 26 patients (20%) started darunavir with an undetectable viral load (that is, patients were already on a successful salvage therapy). Among those starting darunavir with a detectable viral load, 52 patients were followed for at least 48 weeks, with 11 (21%) experiencing virological failure and seven (13%) discontinuing darunavir before 48 weeks. These comparisons suggest that salvage therapy with darunavir is as successful in clinical practice as it has been in clinical trials.

Our time to event analyses suggest that patient health is probably not critical to the success of salvage therapy with darunavir but genotypic resistance clearly is. The overall GSS when starting salvage therapy is predictive of virological failure, if failure is defined as an inability to achieve and maintain viral suppression regardless of whether a patient remains on darunavir. However, simple clinical alternatives seem just as predictive of virological failure. The SHCS resistance database contains all genotypic HIV resistance tests performed by the four authorized laboratories in Switzerland and tests are widely used, with a median of four polymerase tests available for each patient in our sample. However, most patients started treatment for HIV infection many years before resistance testing was available. Our results suggest that, in this situation, treatment history is at least as informative as an overall GSS and could be used to identify individuals who need close monitoring when starting a salvage therapy with darunavir or to serve as a warning that other treatment options might be a better choice. Age and female gender are almost certainly beneficial and probably harmful, respectively, as in PLATO II, where better adherence and health-seeking behaviours among older patients and male homosexuals are suggested as the most likely explanations for these associations [18]. So adherence seems important but past reported nonadherence is a weak predictor of the subsequent failure of salvage therapy.

Both the success of first-line therapies and the success of subsequent salvage therapies are good news for patients but make it difficult to compare salvage therapies or determine factors associated with the failure of such therapies. The slow recruitment of suitable patients and infrequent failure of therapy make it difficult to carry out randomized trials [25]. A Bayesian approach to analysis provides a coherent framework for learning from these slowing accumulating failures, although in time multicohort collaborations such as PLATO may make this approach redundant. The approximate Bayesian method used here is appropriate for 'the imprecise data and goals of everyday epidemiology (which is largely only semi-quantitative inference about an adjusted risk comparison)' [26]. Hence we summarize results using semi-quantitative statements of clinical meaning to show what a clinician might learn from these few failures [27].

Our Bayesian estimates are not very different from the usual maximum likelihood estimates. This should reassure clinicians who worry that the ''use of Bayesian procedures will set the stage for the entry of non-fact-based information that, unable to make it through the 'evidence-based' front door, will sneak in through the back door of 'prior distributions' '' [28]. The key is to use vague, but not uninformative, prior distributions – the statistical equivalent of keeping an open mind. Where there is sufficient information in the data, the prior has no influence (on continuous predictors such as age, viral load and CD4 cell count; Table 3). Where there is less information, the influence of the prior is often subtle, curbing the more extreme limits of the maximum likelihood estimate (as in the upper limit of the CI for female patients; Table 3), but is sometimes obvious (as in the upper limit of the CI for resistance to darunavir under variants 1 and 2; Table 4). One would not usually expect reliable maximum likelihood estimates given a model with six or seven predictors and only 18 to 29 events. As a rule, time to event analyses require 10 to 15 events per predictor [29]. With too few events, maximum likelihood estimates are often biased away from the null value (a hazard ratio of 1) [30]. A well-chosen prior will limit this sparse data bias, constraining posterior estimates to lie within a plausible range by assigning essentially zero prior probability to extreme values. The usual maximum likelihood estimates are just extreme Bayesian estimates using completely uninformative priors where extreme hazard ratios (such as ratios of 20) are seen as just as likely as ratios that are clinically far more plausible in studies of this sort (such as ratios of 1 or 2) [26].

In other similar studies of darunavir, there is evidence of sparse data bias in estimates of odds ratios [31,32]. It is hard to find a study of risk factors for virological failure in salvage therapy that does not involve stepwise variable selection, variable selection based on the results of univariate tests or the fitting of overly simplistic models; yet these strategies lead to models and estimates that are not reliable and do not replicate [29,33]. Invariably some covariates are omitted in an attempt to more reliably

estimate others. Omitting covariates is equivalent to a very strong and often unreasonable prior opinion that the omitted covariates have no effect at all on outcome. A better strategy is to retain covariates and use prior information to constrain estimates to lie within a plausible range.

This study suggests that, when used for salvage therapy, darunavir can achieve a similar efficacy and tolerability in clinical practice to that seen in clinical trials. If a patient does not have a resistance test for each previously failed regimen, then the clinician should also consider simple clinical measures such as whether the patient has failed on amprenavir and saquinavir and the number of failed PI regimens when choosing a salvage therapy.

Acknowledgement

This study was financed within the framework of the Swiss HIV Cohort Study, supported by the Swiss National Science Foundation (SNF grant #3345-062041) and by an unrestricted educational grant from Tibotec, a division of Janssen-Cilag Switzerland. The SHCS genotypic drug resistance database is supported by grants from the Swiss National Science Foundation (SNF grant # 3247B0-112594), the SHCS Research Foundation, and the Union Bank of Switzerland. The Basel Institute for Clinical Epidemiology and Biostatistics is supported by grants from santésuisse and from the Gottfried and Julia Bangerter-Rhyner Foundation. We thank Patrick Graham for advice on how to calculate a Bayes factor from a posterior density.

Disclosure

This is an abbreviated version of a report prepared for Janssen-Cilag Switzerland, based on a project proposal (SHCS 546) approved by the Scientific Board of the Swiss HIV Cohort Study. Janssen-Cilag Switzerland had the opportunity to comment both on drafts of the project proposal and on a draft of the report. The analysis and its interpretation were carried out independent of the company and the scientific content of the report represents the independent opinion of its authors. The project proposal and report and drafts of these documents are available from the first author on request.

Appendix: members of the Swiss HIV Cohort Study

M. Battegay, E. Bernasconi, J. Böni, H.C. Bucher, P. Bürgisser, A. Calmy, M. Cavassini, R. Dubs, M. Egger, L. Elzi, M. Fischer, M. Flepp, A. Fontana, P. Francioli (President of the SHCS), H. Furrer (Chairman of the Clinical and Laboratory Committee), C.A. Fux, M. Gorgievski, H.F. Günthard (Chairman of the Scientific Board), H.H. Hirsch, B. Hirschel, I. Hösli, C. Kahlert, L. Kaiser, U. Karrer, C. Kind, T. Klimkait, B. Ledergerber, G. Martinetti, B. Martinez de Tejada, N. Müller, D. Nadal, F. Paccaud, G. Pantaleo, A. Rauch, S. Regenass, M. Rickenbach (Head of Data Center), C. Rudin (Chairman of the Mother & Child Substudy), P. Schmid, D. Schultze, F. Schöni-Affolter, J. Schüpbach, R. Speck, P. Taffé, A. Telenti, A. Trkola, P. Vernazza, R. Weber and S. Yerly.

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